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Celiac plexus neurolysis: systematical review

Neurolisis del plexo celíaco: una revisión sistemática

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Resumen

Introducción: La mayoría de los pacientes con cáncer desarrollarán dolor crónico. El tratamiento tradicional sigue la escalera de tres pasos de la OMS para el alivio del dolor por cáncer. Sin embargo, este tratamiento tiende a ser ineficaz con el tiempo. A medida que la enfermedad progresa, se necesitan dosis más altas de opioides para lograr un control óptimo del dolor, aumentar los efectos adversos relacionados con ellos y afectar la calidad de vida. La neurólisis del plexo celíaco (CPN) es um método alternativo de analgesia que puede ser extremadamente útil para esos pacientes. **Objetivo:** El objetivo de este trabajo es evaluar la efectividad de la CPN en el control del dolor crónico y revisar su técnica. **Métodos:** Las bases de datos PUBMED, MEDLINE y LILACS se utilizaron para realizar una revisión sistemática, utilizando el impacto como criterio de selección. Los veintiún artículos que seleccionamos se organizaron en una tabla para el análisis estadístico. **Resultados:** La mayoría de los estudios concluyeron que la CPN es un método efectivo para el control del dolor crónico en la parte superior del abdomen y disminuye el consumo de opioides, aunque su efectividad depende del tiempo de administración y la progresión de la enfermedad. **Discusión:** la CPN es un procedimiento quirúrgico que destruye las fibras neurales del plexo celíaco, responsable de la inervación sensible de las vísceras abdominales superiores. Como resultado, las vías aferentes del dolor visceral se bloquean, disminuyendo el dolor. Los pacientes que sufren de dolor crónico originado en la parte superior del abdomen debido a cáncer pancreático, pancreatitis crónica, cáncer gástrico, cáncer hepático metastásico, cáncer biliar, cáncer esofágico u otras patologías que involucran las vísceras abdominales superiores pueden beneficiarse del procedimiento. Múltiples enfoques están disponibles; los posteriores están asociados con menos daño de los órganos viscerales y complicaciones neurológicas. Los enfoques guiados por imágenes que utilizan tomografía computarizada están relacionados con mejores resultados. Las complicaciones son raras, se pueden encontrar complicaciones graves en menos del 2% de los pacientes. **Conclusión:** Los médicos deben considerar la CPN como un posible método de control del dolor para pacientes con dolor crónico originado em las vísceras abdominales superiores. Aunque el impacto en las escalas de mortalidad y dolor puede ser comparable al tratamiento analgésico convencional, este procedimiento es preferible a los pacientes debido a la menor cantidad de efectos secundarios y la disminución en el consumo de opioides.

Palabras clave: Neurólisis del plexo celíaco, vísceras abdominales superiores, dolor crónico, abdomen superior.

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Abstract

Introduction: The majority of patients with cancer will develop chronic pain. The traditional treatment follows the WHO three-step ladder for cancer pain relief. However, this treatment tends to become ineffective with time. As disease progresses, higher doses of opioids are needed to accomplish an optimal control of pain, increasing adverse effects related to them and affecting quality of life. Celiac Plexus Neurolysis (CPN) is an alternative method of analgesia that can be extremely helpful for those patients. **Objective:** The goal of this paper is to evaluate the effectiveness of CPN in chronic pain control and review its technique. **Methods:** The PubMed, MEDLINE and LILACS databases were used to perform a systematic review, utilizing impact as selection criteria. The twenty-one papers we selected were organized in a table for statistical analysis. **Results:** The majority of studies concluded that CPN is an effective method of chronic pain control in the upper abdomen and decreases opioid consumption, although its effectiveness depends on time of administration and disease progression. **Discussion:** CPN is a surgical procedure that destroys the neural fibers from the celiac plexus, responsible for the sensitive innervation of the upper abdominal viscera. As a result, the afferent pathways of visceral pain are blocked, decreasing the pain. Patients that suffer from chronic pain originated in the upper abdomen due to pancreatic cancer, chronic pancreatitis, gastric cancer, metastatic hepatic cancer, biliary cancer, esophageal cancer or other pathologies involving the upper abdominal viscera can benefit from the procedure. Multiple approaches are available; the posterior ones are associated with less damage of visceral organs and neurological complications. Image-guided approaches using computed tomography are related to better results. Complications are rare, serious complications can be found in less than 2% of patients. **Conclusion:** Physicians should consider CPN as a possible pain control method for patients with chronic pain originated in the upper abdominal viscera. Even though impact in mortality and pain scales may be comparable to conventional analgesic treatment, this procedure is preferable to patients due to fewer side effects and decrease in opioid consumption.

Key words: Celiac Plexus Neurolysis, upper abdominal viscera, chronic pain, upper abdomen.

Introduction

More than 50% of patients with cancer will experience physical pain[1]. According to the World Health Organization (WHO) this condition should be treated using the three-step ladder for cancer pain relief, created in 1986[1]. This ladder suggests that the initial treatment consists of nonopioids (aspirin or paracetamol), followed by mild opioids (codeine) and at last strong opioids (morphine). Although this ladder can be extremely effective for some patients, others are not as lucky. As disease progresses, so does the pain, demanding higher doses of opioids. These doses are associated with multiple adverse effects, such as respiratory depression, nausea, vomiting, constipation, hyperalgesia, drowsiness, itching, memory loss, nightmares, myoclonic jerks, tolerance and physiological dependence[2]. These effects can be extreme to the point that patients are unable to continue treatment.

Celiac Plexus Neurolysis (CPN) comes up as an alternative to these patients. CPN is a procedure that can be performed in patients with chronic pain in the upper abdomen. Pain etiology is generally cancer (in the stomach, esophagus, pancreas, biliary tract, small intestine, ascending colon, transverse colon, kidneys or liver metastasis) or nonmalignant chronic diseases, as chronic pancreatitis. Initially described as a surgical anesthesia by Kappis in 1914[3], CPN suffered a change of utility during the mid-20th century, becoming a pain management surgical procedure.

The technique consists in destruction of neural fibers from the celiac plexus, responsible for the sensitive innervation of the upper abdominal viscera. As a result, the afferent pathways of visceral pain are blocked. As the pain subsides, patients become less dependent in opioids, diminishing habitual doses and their adverse effects.

The aim of this review is to address the literature on the real effectiveness of CPN and the impact it has in patients' quality of life. Furthermore, the main aspects related to the procedure are going to be reviewed.

Methods

The PUBMED, MEDLINE and LILACS databases were searched for manuscripts related to management of chronic pain and celiac plexus neurolysis. All articles found relevant were included in this review. Also the reference sections of these articles were evaluated and papers that provided important information regarding the subject were included. The conclusion of these articles was summarized in a chart. All types of study were accepted, including other literary reviews. Articles that did not provide data regarding effectiveness of the technique were not included.

Results

Twenty-one articles were included in this review, totalizing 2,442 patients. The articles were written between 1996 and 2019. All data collected was summarized in Table 1, including the conclusion, year and number of patients evaluated. We noted that in the last few years, the number of papers regarding CPN drastically decreased. Although, the number of papers concerning specifically Endoscopic-Ultrasound Guided Celiac Plexus Neurolysis (EUS-CPN) increased significantly, showing a new tendency in research related to this subject.

Table 1. Celiac Plexus Neurolysis: a systematic review			
Author	**Number of Patients**	**Year**	**Conclusion**
Mercadante S.[16]	20	1993	Equal reduction of pain in comparison to analgesic drugs, however with fewer adverse effects
Eisenberg E, Carr DB, Chalmers TC.[18]	989	1995	89% of patients presented excellent or good pain relief in the first two weeks after treatment
Kawamata, et al.[21]	21	1996	Provides reduction of morphine consumption and reduces the deterioration of quality of life
Polati E, Finco G, Gottin L, et al.[22]	24	1998	Reduction in analgesic drugs consumption and side effects related to them
Gress F, et al.[10]	22	1999	Appears to be a safe and effective method for controlling abdominal pain that can accompany chronic pancreatitis
Rykowski JJ, Hilgier M.[13]	50	2000	Pain relief in 74% of patients with pancreatic cancer pain
Gunaratnam NT, et al.[23]	58	2001	78% of patients experienced a decline in pain scores
Vranken JH, Zuurmond WW, de Lange JJ.[24]	12	2001	Improves quality of life and provides significant pain reduction, however has a short-lasting analgesic effect
Okuyama M, et al.[25]	21	2002	Effective pain control and reduced opioid consumption
De Oliveira R, et al.[7]	60	2004	Improves quality of life and reduces cancer pain, analgesic consumption and adverse opioid-related side effects
Wong GY, Schroeder DR, Carns PE, et al.[26]	100	2004	Better pain relief than systemic analgesic therapy alone, however it does not affect quality of life and survival
Jain, et al.[27]	100	2005	Better pain control and reduction in opioid consumption
Ramirez-Luna MA, et al.[28]	11	2008	Pain improvement in 72% of patients after 4 weeks of procedure
Puli, et al.[11]	283	2009	Pain control in 80.12% of patients with pancreatic cancer
Erdek, et al.[8]	50	2010	May provide intermediate pain relief to a significant percentage of patients suffering from pancreatic cancer
Arcidiacono, et al.[24]	358	2011	Pain relief minimally superior than analgesic therapy, however with fewer adverse effects
Yang FR, et al.[30]	12	2012	Provides analgesia and reduces morphine consumption and the adverse effects related to it
Seicean A, et al.[31]	32	2013	Pain improvement in 75% of patients
Malik, et al.[36]	35	2018	Decrease in pain score and analgesics use
Lou S.37	58	2019	Response rate of 79,3%
Facciorusso, et al.[14]	156	2019	87,1% of patients achieved pain relief
Galafassi, et al.: Celiac Plexus Neurolysis: A Systematic Review.			

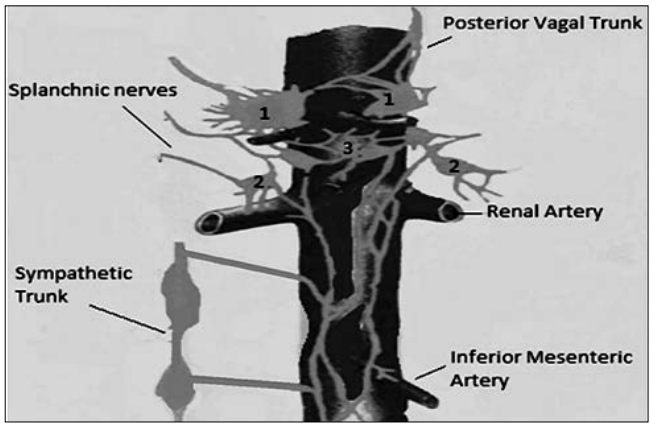

Figure 1. Celiac Plexus Anatomy. Celiac ganglia (1), aorticorenal ganglia (2) and superior mesenteric ganglia (3).

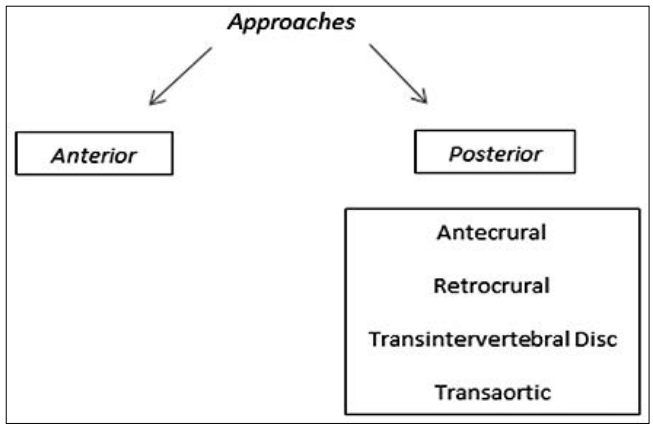

Figure 2. Types of Approach.

Table 2. Anatomic Considerations
Largest visceral plexus
Located in the retroperitoneal space, over the celiac trunk and superior mesentery artery
Composed of preganglionic sympathetic efferent nerve fibers, preganglionic parasympathetic nerve fibers and visceral afferent fibers
Crus of diaphragm separates the plexus from the vertebral column
Posterior to the stomach, left renal vein and pancreas
Anterolateral to the aorta
Composed of celiac, superior mesentery and aorticorenal ganglia
Number of celiac ganglia may vary between 1 to 5, the average size is 2,7 cm
Ganglia can be found between T12 to L2 level
The left ganglia is located below the right ganglia
The left ganglion is located at the origin of the splenic artery
The right ganglion is posterior to the vena cava
Crus of diaphragm (“crura”) separates two zones: retrocrural (above L1) and antecrural (below L1)

We express our results in Table 1, summarizing all important articles showing that a decrease in chronic pain was achieved in 82,4% of cases, according with the literature (minimal 72% to 89%) in 2,442 cases.

Discussion

Celiac plexus is the largest visceral plexus, located anterior to the celiac trunk and superior mesenteric artery, at the level of T12 or L1[5]. In Figure 1 it is possible to observe the anatomy and its relationship with aortic structures. There may be one to five ganglia present, measuring between 0.5 and 4.5 cm in diameter[6]. The plexus contains sympathetic fibers from the greater (T5-T9), lesser (T10-T11) and least (T12) splanchnic nerves, parasympathetic fibers, from the celiac branch of the vagus nerve, and sensory afferent fibers, responsible for conduction of nociceptive stimuli. Celiac Plexus supplies all types of fibers to the upper abdominal viscera, including liver, gallbladder, biliary tract, pancreas, spleen, stomach, mesentery, bowel to the level of proximal transverse colon, kidneys, adrenals and abdominal blood vessels.

These anatomic and physiological aspects explain why CPN can effectively control the pain originated in upper abdomen. In Table 2, the main aspects of anatomy can be clarified. Possible etiologies for this condition are pancreatic cancer, chronic pancreatitis, gastric cancer, metastatic hepatic cancer, biliary cancer and esophageal cancer.

A major factor that needs to be clarified is that pain is a complex entity that generally involves multiple aspects, including psychological ones. Therefore, a state of complete pain absence is highly difficult to accomplish. CPN essentially modulates pain transmitted through celiac plexus fibers, so pain originated in abdominal wall or pelvis, not transmitted through celiac plexus, will not be extinguished. Although it may seem obvious, most patients do not understand this concept, which may cause unreachable expectations.

The effectiveness of CPN is directly related to disease progression and time of administration[7,8,9]. Some authors believe it should be performed at disease initial stages, since

Table 3. Advantages and Disadvantages of the Main Approaches		
Approach	Advantages	Disadvantages
Anterior	Low risk of neurological injury and reduced patient discomfort	Higher risk of infection, hemorrhage and fistula formation due to visceral organ injury.
Retrocrural (Figure 7)	Traditional technique, can be used if the pre-aortic space has anatomic distortions	Higher risk of kidney, liver, pleura or major vessels injury
Antecrural (Figure 7)	Can be performed with a single needle and provides highly effective pain control	Uses higher doses of neurolytic agent.
Transintervertebral Disc	Can be used in patients with degenerative disease of the thoracolumbar spine	Higher risk of disc trauma, spinal cord injury, aortic puncture and retroperitoneal hematoma
Transaortic	Lower risk of neurologic complications	Increased risk of retroperitoneal hemorrhage and aortic puncture

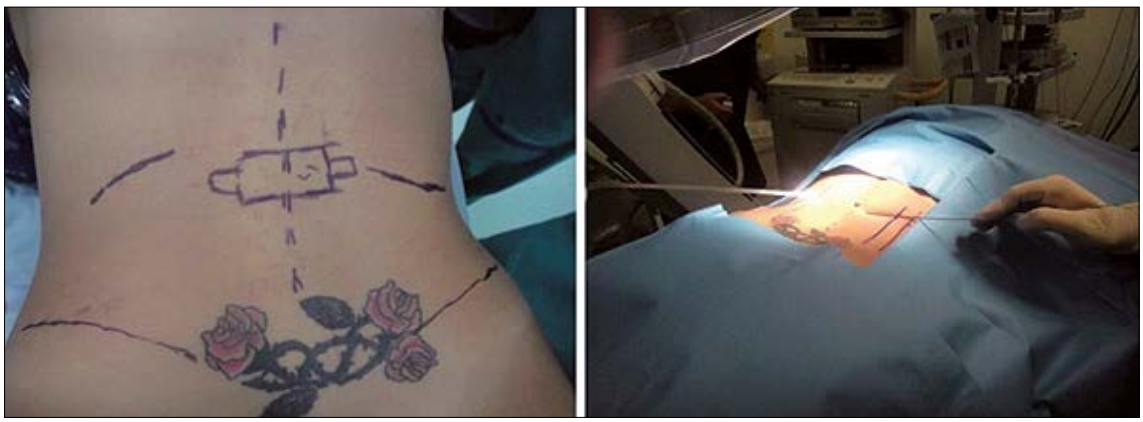

Figure 3a. Patient under general anesthesia and orotracheal intubation in abdominal horizontal position; 3b: CPN guided by fluoroscopy, showing the insertion of the needles (pictures by Thania González Rossi).

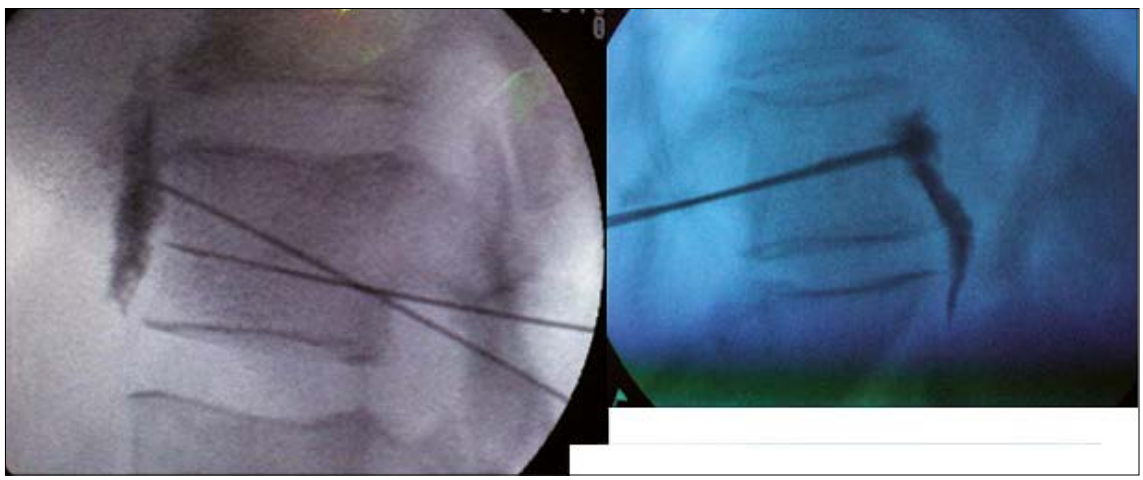

Figure 4a. Two needles are inserted till the front of vertebral body of L1 below the transverse apophysis, 15 mL to 40 mL of ethanol may be administered; 4b: Iliohypograstric plexus can also be reached in the level L3/L4 (pictures by Thania Gozález Rossi).

somatic components of pain (not transmitted through celiac plexus) are not as present in comparison to more advanced diseases, also opioid consumption is not as high. High opioid consumption has been associated with more aggressive tumors, less favorable disease state, nociceptor sensitization, poor coping skills, depression and catastrophization[8]. Therefore, decrease in opioid consumption is one of CPN results that impacts quality of life the most. As disease progresses pain arises, so CPN effectiveness tends to decline. A new procedure may be performed, even though success is not guaranteed. Repeated CPN is related to less than satisfactory pain control and decreased durability. The main approaches for CPN are showed in Figure 2, where an anterior approach or posterior approach can be showed. The anterior approach can be performed through open surgery, endoscopic, or by laparotomy and the posterior by minimal invasive approaches with needles laterally to the vertebral body and transdiscal, all guided by fluoroscopy. The main advantages and disadvantages as well as complications may be observed in Table 3.

Technique also interferes with CPN effectiveness. Multiple

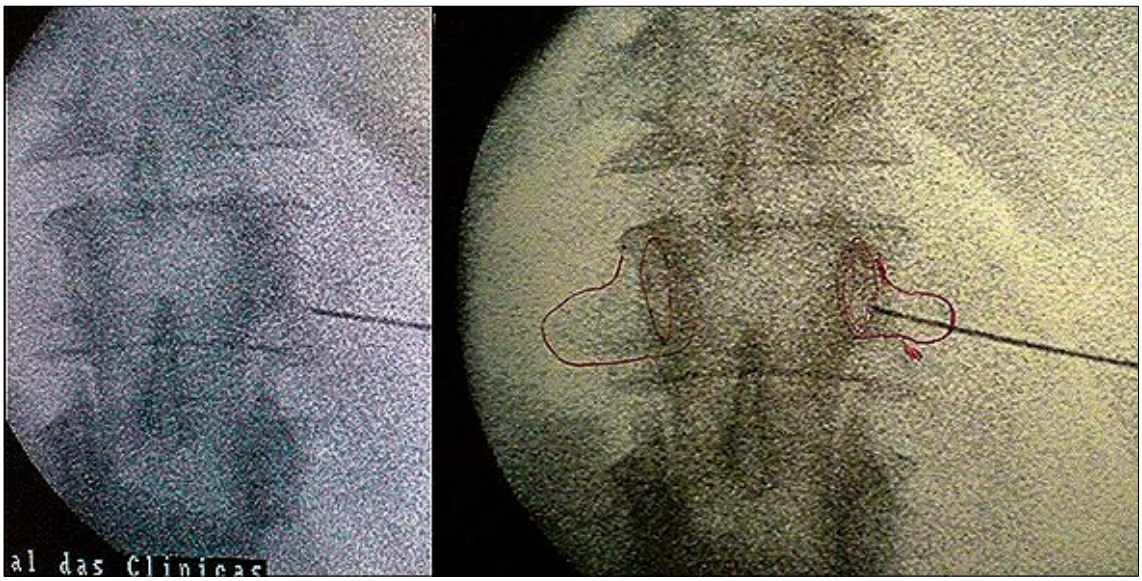

Figure 5. Anterior screen view to identify the level L1 and transverse apophysis (pictures by Thania González Rossi).

Figure 6. Surgical view of needle placement in the level L1 bilaterally, guided by fluoroscopy (picture by Thania González Rossi).

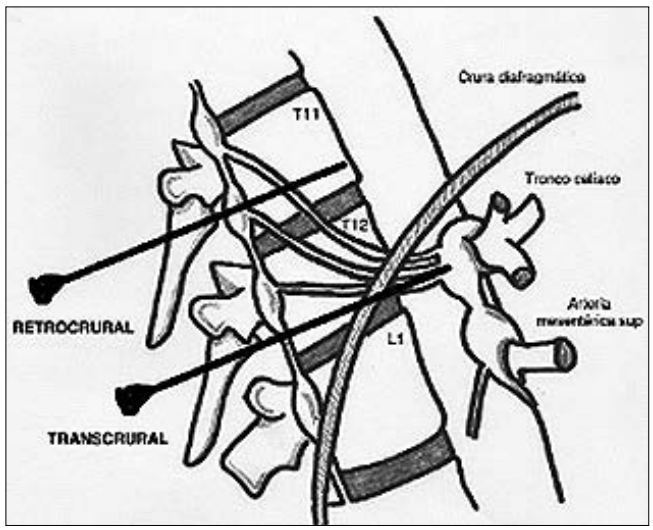

Figure 7. Image from "Revisión de los procedimientos intervencionistas neurolíticos en el dolor asociado al cáncer de páncreas. Propuesta de algoritmo" Manuel Herrero Trujillano Agustín Mendiola De La Osa, Joaquin Insausti Valdivia, Juan Pérez Cajaraville. Revista de la Sociedad Española del Dolor December 2019 DOI: 10.20986/resed.2019.3715/2018.

types of approach have been described, but the posterior ones are associated with less damage of visceral organs and neurological complications[9]. The posterior approaches are: antecrural (Figure 7), retrocrural (Figure 7), transinterverte-bral disk and transaortic. Image-guided approaches may be performed using fluoroscopy, ultrasound, or computed tomography (TC), although TC generally correlates to better results, seeing that it enables good tissue distinction, pre-procedure planning, intraprocedure needle tip localization, and direct visualization of contrast diffusion. Magnetic resonance can also be used, but at increased costs[10,11]. The latest approach described is endoscopic ultrasound-guided celiac plexus neurolysis (EUS-CPN). EUS-CPN has fewer complications (especially when performed associated with color Doppler technology[12]), better results and is preferable to patients than the percutaneous approach[13]. EUS-CPN can be extremely beneficial for pancreatic cancer patients[14]. EUS-guided celiac ganglia neurolysis and EUS-guided broad plexus neurolysis consist in variations of EUS-CPN. These procedures intend to improve effectiveness of the traditional EUS-CPN method[12].

CPN is generally performed using an injection of 50 to 100% ethanol, associated with bupivacaine and iodinated contrast (Figures 3-6). Ethanol produces irreversible neural damage by extracting cholesterol, phospholipids and cerebroside from neurolemma and causing immediate precipitation of endoneural lipoproteins and mucoproteins[9]. This effect can be achieved in concentrations above 50%. From this point, destruction is not directly associated with concentration, but with

the distribution of the neurolytic agent[9]. The association with bupivacaine, or another long-acting local anesthetic, prevents severe temporary pain related to ethanol injection. To facilitate the visualization of neurolytic distribution, iodinated contrast may be used[9,15]. Ethanol volume varies between 15 to 50 mL depending on approach and number of needles (unilateral or bilateral) (Figures 3-6). Phenol 3 to 10% is another neurolytic that can be used; however it has a shorter duration and is less effective than ethanol[16,9,15]. Number of needles may vary. Single needle approaches are related to faster procedure time and fewer block failures[17].

CPN complications are rare, serious complications occur in less than 2% of patients[16,18]. Possible complications are back pain (tends to resolve in 72 hours after procedure), hypotension (decreased sympathetic action causes vasodilation), diarrhea (due to imbalance between sympathetic and parasympathetic fibers, resulting in increased peristaltic activity and decreased intestinal transit time)[9,6], paraplegia, paresthesias, dysesthesia in the groin, anal and bladder sphincter dysfunction, impotence, fever, pleuritis, pericarditis, pneumothorax, arterial dissection, superior mesenteric vein thrombosis, hematuria, aortic pseudoaneurysm, retroperitoneal fibrosis and abscess, gastric necrosis and perforation[9,6]. Long-lasting hypotension and constipation can also be found19. CPN contraindications are: patients with increased risk of bleeding (coagulopathy or thrombocytopenia), aortic mural thrombosis, abdominal aortic aneurysm, ongoing infection or abnormal anatomy obscuring the trajectory of the needle[20].

Conclusion

NCP is an effective and secure procedure that should be considered a first-line therapy for refractory pain in upper abdominal viscera. Even though NCP and conventional analgesic treatments seems to affect pain scale and mortality similarly, NCP has fewer adverse effects. Reduction in opioid consumption is an advantage of NCP that definitely improves quality of life. Therefore, the beneficial aspects of this procedure would be a significant increase in quality of life, reduction in analgesic use and reduction of adverse effects related to opioid chronic use.

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